PROTECTING HUMAN SUBJECTS

U.S. DEPARTMENT OF ENERGY, OFFICE OF BIOLOGICAL AND ENVIRONMENTAL RESEARCH

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Contacting us

The *Protecting Human Subjects* newsletter can be found on the internet at **www.science.doe.gov/ober/humsubj/newslett.html**

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Organizational Ethics

Carol Taylor's goal is institution–wide integrity

It is important, Sister Carol Taylor says, that people involved in any organization remember that they have special obligations that accrue from the nature of the relationship between them and others.

Sister Carol Taylor

An ethicist and director of Georgetown University's Center for Clinical Bioethics, Taylor is also an assistant professor of nursing at Georgetown and a member of the hospital's ethics committee.

She says the ethical climate developed by the leadership of an institution is as important as the commitment to ethical practice made by researchers, clinicians, or others.

Because of this, Taylor emphasizes the importance of organizational ethics during ethics seminars she leads.

"Organizational ethics," she explains, "is the intentional use of values to guide the decisions of a system. The objective is to develop a strong fit between the system's stated mission and decision making at all levels of the system.

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New Beryllium IRB

Unique IRB established by DOE

The new Central Beryllium Institutional Review Board (CBeIRB) met December 17–18, 2001, in Knoxville, Tenn.

The Board was established earlier in the year by the U.S. Department of Energy's (DOE's) Office of Science with support from the Office of Environment, Safety and Health.

The group is designed to assist DOE in assuring effective, consistent, and continuing protection of human subjects involved in research on the biological and clinical effects of exposure to beryllium across the Department. In this capacity it will review all beryllium-related projects involving human subjects for all DOE sites. The board will also provide advice as requested on bioethics issues in beryllium communications to workers, researchers, and local IRBs.

Unique concept

The concept of a central IRB is unique in the interagency human subjects community. It follows the

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Moral agency involves a set of competencies: moral sensibility, responsiveness, reasoning, accountability, character, valuing, and transformative moral leadership.

Integrity is broader, deeper, and more demanding than a legal compliance initiative.

For example, 'moral agency' should be a criterion for hiring, advancement, rewards, sanctions, and firing for all senior management.

'Moral agency' means the capacity to habitually act in a manner consistent with moral integrity, and this entails a set of competencies: moral sensibility, responsiveness, reasoning, accountability, character, valuing, and transformative moral leadership."

She says a stated policy about these issues is necessary because one cannot presume that everyone in an organization will act ethically.

Won't take care of itself

"This is not something that will take care of itself. That assumption isn't working, as our experience makes painfully clear."

Health care and research work best, Taylor believes "when everyone involved in the design and implementation—including administration, financing, and evaluation—understands the moral nature of the work and the ways they can explain and justify moral choices."

She says several factors are involved in making any entity act with integrity, whether it is a profession, an institution, a system, or a country.

"It takes a commitment to developing and owning a conception of the Good, that is, a commitment to creating a morally good version of whatever it is we're doing.

This includes the way we think about the work, make decisions, relate to others, work to improve health care or research, and the way we integrate professional and personal responsibilities."

It sometimes seems to people that compliance with existing regulations, laws, mandates, etc., is sufficient to claim integrous behavior, but is not, Taylor says.

Ethics, not just compliance

There is a difference between ethics and compliance, she said. Compliance is predominantly lawyer driven and merely meets basic legal requirements. "The goal is to prevent, detect, and punish legal violations. Even at its best it is unlikely to unleash much moral imagination or commitment. The law doesn't generally seek to inspire either human excellence or distinction and so it is no guide for exemplary behavior, or even good practice."

An integrity-based strategy, however, emerges from the organization's values and is implemented by a broader base of management and leadership. "It is characterized by a conception of ethics as a driving force of an enterprise."

She said ethical values shape the search for opportunities, the design of organizational systems, and the decision-making process. They provide a common frame of reference and serve as a unifying force across the organization.

Ethics defines the institution

"Organizational ethics helps define what an institution is and what it stands for. Integrity is broader, deeper and more demanding than a legal compliance initiative."

It is broader, she explained, in that it seeks to enable responsible conduct. It is deeper in that it cuts to ethos and operating systems of the organization and its members, their guiding values and patterns of thought and action. And more demanding in that it requires an active effort to define the responsibilities and aspirations that constitute an organization's ethical compass.

To develop an integrity-based organization requires that the group articulate and reflect on a set of values and accept them for the organizational culture they are trying to create.

Set aside time and space
Taylor said this requires that the organization set aside time and space and that the values be looked at periodically to ensure they remain relevant and "fresh."

Some organizations focus on values that reflect basic social obligations such as respect for the rights of others, honesty, fair dealing, and obedience to the law. Others emphasize aspirations—values that are ethically desirable but not morally obligatory, such as service to customers, commitment to diversity, and involvement in the community.

It is important, she said, to identify one person who will be ultimately responsible for the ethics program and a core team, or teams, of those who will help develop the structures that facilitate education, implementation, consultation, auditing, and evaluation.

Also important is to clarify relationships among and appropriate mechanisms for addressing clinical, business, workplace, and research ethics.

And she says it is "absolutely essential" for those charged with responsibility for the program to be perceived as "authentic" in regard to the mission and core values, in their personal, professional, and institutional lives. That person also must possess ethical expertise that is useful.

Senior management must from the outset understand and wholeheartedly support the program, she said, including having a willingness to fund it.

Some fear the idea
"It is not uncommon for key institutional leaders to fear the whole idea," she said, "because of concern about what issues will be raised."

A simple mechanism to get information about the sensitivity to ethics among all employees is to implement a survey questionnaire with questions that are relevant to their work.

One way to help the program become a part of the organizational culture is to develop a "Best Practices" forum to affirm and reward outstanding achievement. It is also helpful, she said, to impose consequences for poor behavior.

Finally, among the ways to tell that you have a successful program is when there is the feeling in the organization that decision-making at all levels is aligned with the vision, that there are no mixed messages.Δ

Some organizations focus on basic social obligations. Others emphasize aspirations.

Senior management must from the outset understand and wholeheartedly support the program.

Human subjects protection Web sites

Human Subjects Research Training, sponsored by The Collaborative IRB Training Intiative (CITI) and The University of Miami
http://www.miami.edu/bb/citireg/

Office for Human Research Protections (OHRP), Department of Health and Human Services *http://ohrp.osophs.dhhs.gov/*

National Human Research Protections Advisory Committee (NHRPAC)
http://ohrp.osophs.dhhs.gov/nhrpac/nhrpac.htm

Human Subject Protections - IRB Guidebook, OHRP
http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm

National Standards to Protect the Privacy of Personal Health Information
http://www.hhs.gov/ocr/hipaa/

Responsible Mandates

By Kenneth Pimple
Director of Teaching Research Ethics Programs
Poynter Center for the Study of Ethics and American Institutions

If there are any fields in which poor training is better than no training, research ethics is not one of them.

Knowing regulations is necessary but not sufficient to ensure adequate compliance.

It seems likely that everyone who reads this newsletter knows about the most recent training mandates from the federal government:

As of October 1, 2000, the National Institutes of Health (NIH) has required "education on the protection of human research participants" for all NIH investigators whose research involves human subjects. See: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

On December 1, 2000, the Office of Research Integrity (ORI) unveiled its final "Policy on Instruction in the Responsible Conduct of Research (RCR)," requiring that "research staff . . . at extramural institutions shall complete a basic program of instruction in the responsible conduct of research" covering nine subject areas. See: http://ori.dhhs.gov/html/programs/rcr_requirements.asp.

The ORI mandate was suspended in February 2001 but will undoubtedly resurface.

Counterproductive?

I train researchers in RCR and in teaching research ethics for a living. Over the past ten years, I have said repeatedly that teachers of research should teach the responsible conduct of research. Yet I fear that ORI's RCR training mandate may be counterproductive.

While I favor pervasive RCR education (I use "training" and "education," as well as "research ethics" and "RCR," as synonyms), it should be high-quality training provided by enthusiastic researchers, not a cursory effort grudgingly thrown together to comply with a mandate. If there is any field in which poor training is better than no training, research ethics is not it.

What does the government hope to accomplish in mandating RCR education?

Stamp out misconduct?

Is it to stamp out all misconduct? This is obviously an unattainably high standard. As for merely reducing misconduct—well, there will be no way to tell whether we have because our baseline data are so poor that we don't know how common misconduct is.

Many people seem to take eliminating or reducing misconduct as the obvious and only goal of RCR training. Once when I was interviewed by a journalist about research ethics education, she mentioned the high-profile case of a young researcher who had fabricated data for a series of publications that were subsequently retracted. She added, in a weighty tone, that he had taken a course in research ethics. I pointed out that he had taken *many* courses in science. Which had failed, his training in science or in research ethics?

Increase moral reasoning?

Are we expected to increase our trainees' moral reasoning ability? The policy doesn't say so, but this is one aspect of ethics education that has been shown to be effective and measurable. Are we expected to ensure that researchers know the relevant regulations? Yes, but that's not all. Clearly knowing regulations is necessary but not sufficient.

I don't know whether anyone has shown that knowing regulations leads to following them, but it is hard to expect people to follow regulations they don't know or understand.

Requiring training in regulatory compliance makes sense, designing and providing the appropriate training would be straightforward, and measuring the success of the training would be fairly simple (if they know the regulations, it works) —though such training would almost certainly be very boring.

Narrow focus

Of course, a narrow focus on regulatory compliance would not cover all nine of the mandated instructional areas because many of them lack guiding regulations.

Indeed, there is not even a clear consensual standard for many, which makes offering authoritative training difficult.

We should certainly adopt a higher standard than that of merely knowing the regulations. Today's graduate students and junior scientists are the rule makers of tomorrow, and they must be thoughtful about research ethics, not mere followers of rules.

Engaging the imagination

RCR education should engage the imagination, cover more than regulations, and prepare researchers to encounter novel moral problems just as they are prepared to encounter novel experimental findings. Research ethics is not about memorizing regulations or rules; it's about having a commitment to doing what's right and the cognitive, emotional, and social skills to succeed.

But how do we measure that? Unfortunately, very little is known about any of the following:

- whether training or education in RCR makes any difference;
- what difference it makes;
- what kind of training (lecture, case study discussion, etc.) makes the most difference; or
- what kind of difference each kind of training makes.

In the absence of this kind of very basic information, research institutions are flying blind.

Intangible goals

It's one thing for a researcher or teacher to pursue intangible or vaguely articulated goals on his or her own; it's another for the government to mandate them.

> "Anything goes" is the worst possible lesson in ethics

When the government orders us to do something, it's only fair for it to tell us how we can know whether we've done it—especially when the government can be expected to punish us when it thinks we have not done it right. If the government can't tell us how to measure our success (or failure), should we be punished for failure? Indeed, ordering us to do something with no guidance on how our efforts will be evaluated amounts to allowing us to do anything. And "anything goes" is the worst possible lesson in ethics.

I should make it clear that I am not opposed to mandatory RCR training per se. The problem arises when the mandate comes from someone too far removed from the folks who have to implement it. Teaching the responsible conduct of research

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New Beryllium IRB

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lead of a model used by the National Cancer Institute to review clinical trials that are conducted at hundreds of sites nationwide.

The CBeIRB is administered by Oak Ridge Associated Universities (ORAU) under its Multiple Project Assurance with the Department of Health and Human Services.

Approval required before work starts

It also oversees Beryllium projects conducted at other institutions with funding support from DOE or other agencies in which DOE or contractor employees are involved as subjects. The board's approval is required before work on any new study involving DOE workers as subjects is started.

Human Subjects Program Manager Susan Rose with Robert Bistline, of the Rocky Flats field office.

Shirley Fry, chair of the new Central BeIRB

The 16 members of the CBeIRB are a stellar group with expertise in occupational and clinical medicine, industry, ethics, law, science, and industrial hygiene. They have representation from the National Institute of Occupational Safety and Health and DOE's operations offices and national laboratories. Michael Jackson is a Be worker and Chronic Beryllium Disease patient. Union member Jim Hendricks also serves on the board.

Shirley Fry is chair

Shirley Fry, MD, chairs the board, which expects to meet three or four times a year. She also chaired The Oak Ridge Associated Universities/ Oak Ridge National Laboratory (ORAU/ORNL) IRB for five years and was a member for 20 years. Becky Hawkins, ORAU, is the board's administrator.

Donna Cragle, of the ORISE Be program, gave a short course on beryllium during the IRB meeting.

From occupational medicine, David Deubner, left, of Brush Wellmann, Inc., talks during a break with David Wehrly, of DOE's Oak Ridge Y-12 complex. Wehrly is vice chair of the Oak Ridge site-wide IRB.

The first meeting

The first meeting included an educational session focusing on human subjects, bioethics and informed consent, regulatory education and implementation, and beryllium disease and science updates.

The board also reviewed protocols and consent material related to five ongoing projects for continuing approval. Its next meeting is scheduled for May 6–7, 2002, in Knoxville.

Twelve beryllium-related projects that have screened more than 16,000 people at 13 sites for sensitivity to beryllium are being reviewed by the CBeIRB.

Current regulations drafted in 1980s

The current human subjects regulations were drafted early in the 1980s to be applied to all federally funded human

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Social, behavioral studies

IRB focus on biomedical research causes problems

By Caroline Miner
IRB Review and Monitoring Coordinator
Federal Bureau of Prisons

Biomedical research is the primary focus of human subjects regulation and discussion. However, researchers in the social and behavioral sciences are held to the same regulatory standards and practices as the biomedical researchers. This causes problems for social and behavioral scientists and the IRBs that review their proposals.

Problems

For example, the Common Rule (CR) requirements for informed consent, while necessary and appropriate for clinical studies, are burdensome for some virtually no-risk social science studies. In some cases, social and behavioral researchers are required to utilize a consent process that is more time consuming than the research.

Also, descriptions of exempt research and the definition of human subject, while perfectly clear for most research, can be quite murky when applied to some forms of social science research. Projects that would not have been considered "human subjects research" in the past are being reviewed today.

These are extreme examples of problems for social science research projects; however, they are indicative of a trend toward excessive regulatory burden and the IRB hyperprotectionism generated in response to the regulatory environment.

Unnecessary burden

While much of the focus of the regulatory community is on strengthening protections for human subjects, there is also growing recognition that we do not want to add unnecessary regulatory burden, that is, regulation or guidance that does not actually result in increased protections for research participants. But often this is exactly what happens because regulations targeting the biomedical community do not always translate well for application to the social science community.

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Projects that would not have been considered "human subjects research" in the past are being reviewed today.

Current human subjects regulations were drafted early in the 1980s to be applied to all federally funded human subjects research.

Beryllium IRB meets

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subjects research projects. The regulations were codified in 1991.

The Office of Science has had responsibility for human subjects research since the first human subject regulation drafted by the Office of Biological and Environmental Research was codified in 1976.Δ

Michael Jackson, a Be worker and member of the CBeIRB

Social, behavioral studies

(Continued from previous page)

The working group encourages readers to submit comments on the ASA web site: www.asanet.org/public/humanresearch/

Input has been gathered from the American Psychological Association, American Anthropological Association, and the American Society of Criminology.

Addressing the problem
Some of the groups working to address this problem include the Social and Behavioral Science Working Group of the National Human Research Protection Advisory Committee (SBSWG-NHRPAC), the Non-Biomedical Working Group of the Human Subjects Research Subcommittee (NBMWG-HSRS), and the Responsible Conduct of Research Education Consortium (RCREC).

NHRPAC created the Social and Behavioral Science Working Group to obtain advice and comments from this community. The group has two primary goals. The first is to develop guidelines to help IRBs more effectively administer the human subjects protection system. The second is to make specific recommendations regarding additions or changes to the CR with respect to the social and behavioral sciences.

Seeking help
To achieve these goals, SBSWG has gathered broad input from researchers and IRB members nationwide by convening forums at Association conventions, including the American Psychological Association, American Anthropological Association, and the American Society of Criminology.

From discussions already held, several problematic issues have been identified, including unnecessary reviews of exempt research proposals involving publicly available data files, a general lack of understanding about how to evaluate risk in social science research.

We have also identified several topics for which guidance is needed:

Identifying and protecting third parties in research, identifying best practices for preserving participant confidentiality, and applying informed consent as a process rather than as a document.

Soliciting input
The working group is soliciting input about these and other issues not yet identified and encourages readers to submit comments on the American Sociological Association (ASA) web site: http://www.asanet.org/public/humanresearch/. As we finalize our recommendations, they will be posted on the web site.

A second group working on the problem of social science research is the NBMWG of the Interagency Human Subjects Research Subcommittee (HSRS).

The HSRS was created to develop and maintain a consistent, uniform interpretation of the CR, and the NBMWG was formed to specifically address the issues of nonbiomedical researchers.

The group is creating a comprehensive decision tree guidance document / web page that is truly a collaborative effort involving representatives from many agencies and disciplines.

Applying the CR consistently
Achieving consistent application of the CR among the various Federal agencies will make it easier for IRBs to navigate the regulatory requirements. It should also eliminate, or at least reduce, incidences of IRBs receiving conflicting regulatory advice from competing agencies.

A newly formed group of representatives from universities, industry, government, and

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Hawkins gets IRB position

Oak Ridge Associated Universities (ORAU) has named Becky Hawkins as the full-time administrator for the Oak Ridge site-wide Institutional Review Board (ORSIRB) and the Central Beryllium IRB (CBeIRB).


Becky Hawkins

Becky has been the Oak Ridge IRB secretary for 16 years. For the past four years, she has been a member of the DOE Human Studies Working Group.

The ORSIRB has oversight of all human subjects studies at all sites under the direction of DOE's Oak Ridge Operations Office.

It also oversees human subjects research conducted by outside organizations on the Oak Ridge work force, including Portsmouth and Paducah, Kentucky, operations. These include university–based organizations.Δ

The IRB has oversight of all human subjects studies at all sites under the direction of DOE's Oak Ridge Operations Office.

Knudson wins writing award


Paula Knudson

Paula Knudson, of the University of Texas Health Science Center, won the 2002 John P. McGovern Award for Outstanding Contributions to Medical Communications. She is a longtime member of DOE's Human Subjects Working Group.

The award is presented by the American Medical Writers Association, Southwest Chapter. At the award ceremony, Knudson presented a lecture titled "The Minefields Surrounding Informed Consent for Research."

Focusing on the "incompleteness" of patient informed consent in the research setting, she addressed several specific questions: Is there such as thing as informed consent? Who, if anyone, is explaining to the patient what is being asked of him or her? Who implements informed consent? By signing a piece of paper, is a patient truly informed?Δ

Knudson talked about "The Minefields Surrounding Informed Consent for Research."

Elliott to be next ARENA head

Marianne Elliott has been named president elect of the Applied Research Ethics National Association (ARENA).


Marianne Elliott

Elliott, now vice president of the group, is in the office of the vice chancellor for research, University of Illinois at Chicago. She has been active nationally in human subjects education and compliance. She is also a consultant to academic and federal agencies.

ARENA is a national organization for professionals concerned with issues relating to the protection of human subjects, humane care and treatment of animals, scientific misconduct, ethics in healthcare, and other ethical issues pertaining to biomedical and behavioral research.Δ

ARENA deals with issues involving human subjects, treatment of animals, scientific misconduct, and research.

8000 students anticipated

Online resource for ethics instruction

By Michael Kalichman
University of California, San Diego

The purpose of the site is to promote the process by which regulations, guidelines, standards, and ethics are reconciled.

Training in the Responsible Conduct of Research is increasingly becoming a legal obligation.

Training in the Responsible Conduct of Research (RCR) is an ethical responsibility and is increasingly becoming a legal obligation. Unfortunately, formal instruction in RCR is not widespread and often suffers from the need to develop new curricula from scratch.

While the necessary materials and programs for RCR instruction are being developed at many institutions, no simple mechanism has been available to make this information widely and easily accessible.

A Web-based resource **(http://rcr.ucsd.edu)** has been developed at the University of California San Diego to disseminate information and options for RCR instruction. Sponsored by the Office of Research Integrity (ORI), the project has been a collaborative effort with colleagues at Virginia Commonwealth University and the University of Minnesota.

The purpose of the site is to promote the process by which regulations, guidelines, standards, and ethics all work together to promote integrity in all aspects of research.

Developing expanded web site

An expanded version of the Web site is being developed that will provide more instruction and additional resources. The expansion will divide the site into four areas: general resources, human subjects, animals, and an interactive section. The sections are:

(1) rcr will contain resources and tools for instruction in all areas of RCR.

(2) rcr/human will contain instruction in responsible conduct of research with human subjects.

- Courses: This area of the Web site will offer links to a selection of effective, online course options and contacts for successful live course formats. Annotations will clearly alert users to the structure and content of each of the courses and intended users.
- Topics: Examples of topics specific to human subjects research include informed consent, social science research, international research, conflicts of interest, and genetics. For each topic, the Web site will provide a brief summary of the relevant issues and a selection of resources for both instructor and trainee.
- Principles, Rules, and Guidelines: The responsible conduct of human subjects research is guided by principles (e.g., Belmont report and Nuremberg code), regulations (e.g., FDA and PHS), and guidelines (e.g., professional and institutional). This area of the Web site will include links and commentary for some of the most important of these principles, rules, and guidelines.
- Cases: The best respected tools for RCR instruction are cases designed to encourage thoughtful discussion of difficult issues. This section of the Web site will provide examples and suggested sources for cases, both real and fictional, on each of the topic areas.

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- Texts: This section will provide an annotated listing of texts useful for human subjects RCR instruction.
- Contacts: This section will consist of a directory of contact information for relevant government agencies, nongovernmental organizations, and RCR instructors.

(3) rcr/animal will contain instruction in responsible conduct of research with animal subjects and will include courses; topics; cases; texts; contacts; and the applicable principles, rules, and guidelines.

(4) rcr/interactive will be a new forum for exchange of current information about instruction in the responsible conduct of research. It is intended to be a primary national resource for RCR instructors. The components are:

- Calendar: A calendar will list dates and contact information for upcoming conferences, workshops, and training sessions.
- News: Announcements of new policies, requirements, and noteworthy events will be referenced and annotated.
- Forum: Once each month, two or more individuals will be invited to contribute brief essays with different perspectives on a question of current interest.
- Discussion Board: Threaded discussions of topics of current interest for interinstitutional discussion of how to both define and teach responsible conduct.
- Questions: Users of the Web site will be encouraged to submit questions to be answered by other instructors of RCR.
- Evaluations: In the coming years, the number of options and resources for teaching RCR is likely to increase dramatically; however, the quality of those products will undoubtedly be uneven. To help users identify some of the best resources, a couple of mechanisms of evaluation will be integrated into the structure of the Web site. An ongoing process will be designed to solicit and summarize evaluations by instructors of RCR.

More than 8000 students

Over the last few months, the average number of user sessions has been between 40 and 70 per day. Based on the very conservative estimates that this will represent only 800 RCR instructors per year, and that each instructor will teach an average of only 10 students per year, the site will have an impact on over 8,000 students of RCR each year.

A catalyst

The site is intended to be a catalyst for defining commonly accepted standards of conduct, identifying the difficult RCR issues, and promoting discussion about these issues.

Those discussions would occur within the Web site (rcr/interactive) as well as during courses of instruction designed with the help of material obtained from http://rcr.ucsd.edu.Δ

The average number of user sessions has been between 40 and 70 per day.

RCR/interactive will be a new forum for exchange of current information about instruction in the responsible conduct of research.

Coming in April:

DOE Conference:
The Community IRB Member—Neighbor and Partner

See calendar on page 19 for details

International studies

Cultural expectations create challenges

By Bree Klotter
Lawrence Livermore National Laboratory

The U.S. review process must be sensitive to the difference between protecting human subjects and imperialistically imposing American values on other countries.

At the time the study was initiated, the Radiological Institute had no human subjects protections program equivalent to an IRB.

Since the late 1980s, Lawrence Livermore National Laboratory (LLNL) scientists have been involved in several international collaborative studies involving human subjects. Each study brought its own set of challenges from both the IRB's and the investigator's perspective. In most cases, the challenges of international studies resulted from different cultural expectations. For example:

1. In some studies, one collaborator might be interested in the science and what s/he can learn about the condition under study, while the other collaborator might be more interested in the immediate potential therapeutic benefits (including access to health care) for subjects.
2. The laws and ethics of human subjects research in other countries may differ significantly from those of the United States, in which case the U.S. review process must be sensitive to the difference between protecting human subjects and imperialistically imposing American values on other countries.

This article briefly describes four of these studies and highlights the specific challenges faced by both the IRB and the investigators.

Radiation Genotoxicity from the Chernobyl Accident—a collaboration between LLNL and the Radiological Institute, St. Petersburg, Russia.

This study, initiated in 1988, involved a collaborative effort to study the effects, if any, of ionizing radiation on the workers who were involved in the day-to-day cleanup activities at the Chernobyl nuclear power plant. Controls and family members were also included in the subject population.

Subjects were asked to provide 1–3 small samples of blood over a period not to exceed three years. The objective of the study was to further the understanding of genetic damage in human cells resulting from exposure to ionizing radiation.

No protection program

At the time the study was initiated, the Radiological Institute had no human subjects protections program equivalent to an IRB. The LLNL investigators, therefore, had to work closely with their Russian counterparts, the LLNL IRB, and with federal regulators at the Office for the Protection from Research Risks (OPRR) at NIH, as well as the DOE's Program Manager for Human Subjects Research, to set up a local review board.

Every effort was made to assure that the Radiological Institute's ethical review process was appropriate for protecting research participants from research risks. Efforts included a review by OPRR of the composition of the newly constituted review board and translation of meeting discussions leading to approval of the projects. The LLNL IRB maintained close contact with the LLNL investigators and provided ongoing guidance on human subjects concerns during the course of the study.

Unexpected problems arose during the recruiting of controls for the study. Because of a long-standing

mistrust of authority figures, including medical doctors, by the average Russian citizen, there was considerable reluctance among healthy subjects to participate as controls.

Skeptical

Healthy subjects were skeptical that "American doctors" would want to study them if, indeed, there was nothing wrong with them. Over time, the trust level improved, but the final data set had fewer controls than originally intended.

Given this and other cultural differences, LLNL investigators realized early on that trial runs would be useful in identifying and resolving potential problems. They used these trial runs to identify additional materials or training which would facilitate the progress of the study.

In the end, the success of this study was a result of committed scientists in both countries who were willing to adapt as needed to changing circumstances.

Evaluation of chromosome damage to uranium workers in Namibia for the assessment of health risk—a collaboration among LLNL, a research laboratory in the UK, and a large employer and a labor union in Namibia, Africa

In 1998, an LLNL researcher was asked to verify the results of an earlier study that had looked at exposures and chromosome damage to miners working at an open cast uranium mine/ore processing plant in Namibia, a small country in southern Africa.

Standing on a platform in front of the Rossing Uranium Mine in Namibia, Africa are, from right, researcher Joe Lucas, chief medical officer Jamie Pretorious, and officials from the mineworkers union.

The mineworkers union and the company, a dominant employer in Namibia, agreed to hire a multinational team of experts to perform a validation study. Because of the high-profile nature of the study, the government's Minister of Health and Social Services was included in the approval process.

No IRBs

Although Namibia has a strong code of ethics, and requires consent of research participants, the concept of an IRB was foreign to them. LLNL IRB required that the investigator set up a Namibian IRB, following federal guidelines. The LLNL IRB evaluated the composition of the local board and felt it provided fair representation of the local community (men vs. women, scientific vs. nonscientific, professional vs. nonprofessional).

Close contact

The LLNL IRB reviewed copies of the protocol and consent form, and received a copy of the Namibian approval letter as part of the LLNL approval process. LLNL maintained close contact with DOE's Program Manager for Human Subjects Research during the initial setup of the Namibian IRB and the subsequent protocol review and approval.

Several challenges were presented by this study and in retrospect, some issues may not have been adequately addressed by the LLNL IRB espe-

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The concept of an IRB was foreign to Namibia, and no formal committee mechanism was in place.

Because of the high-profile nature of the study, the government's Minister of Health and Social Services was included in the approval process.

UK collaborators felt strongly that their consent form did a better job of informing subjects, and were unwilling to change it to reflect U.S. norms.

The issue relevant to this study was whether or not the LLNL IRB should dictate human subjects protection criteria to another country.

cially with regards to the consent process. For example:

1. During preliminary discussions, the researcher noted that all subjects spoke English, and the IRB subsequently approved an English consent form. However, although there is an 85% illiteracy rate in Namibia, there were no provisions in the consent process to assure that subjects could read and/or understand the consent form.
2. The risks identified in the consent form dealt with providing a small blood sample. The potential for coercion in the recruitment of vulnerable subjects (worker population) was not considered.

In the end, the study progressed smoothly, with the Namibian IRB reporting that no complications or problems arose during the study. However, the LLNL IRB recognizes that it must work closely with foreign collaborators to assure that recruitment issues and the consent process are adequately addressed prior to the initiation of subject contact.

Cytogenetic analyses of spermatozoa from testicular cancer patients exposed to radiotherapy—a collaboration between LLNL and the Mexican Institute for Social Security, Mexico City, Mexico

This ongoing, international study, begun in 2000, involves a collaboration between an LLNL researcher and his collaborator at a medical school in Mexico. The study team is investigating the effects of ionizing radiation on semen quality and genetic damage in sperm of patients with testicular cancer who are treated with radiotherapy. Patients who agreed to participate in the study provided semen samples before, during and after radiotherapy treatment.

Relatively effortless

From the IRB's perspective, this collaboration was relatively effortless, perhaps because the Mexican collaborator had spent time at LLNL, and was familiar with the ethics review process here in the United States.

Mexico does have an ethics review process and consent is required of all research participants prior to their enrollment in a study. As part of the original review, the LLNL Board requested and received a copy of the ethics review board approval and a copy of the Mexican consent form.

Translated from Spanish

To verify content, the consent form was translated from Spanish to English by two separate LLNL individuals. As with the UK study mentioned below, not all required elements of 45 CFR 46.116 were included on the Mexican consent. However, it did provide basic information about the research and allowed for a subject to make an informed decision about whether or not he would want to participate in the research.

At the annual review, the LLNL IRB requested and received verification from the Chair of the Mexican ethics review board that the study received continuing review and approval with no comment. Also, at the request of the LLNL IRB, the collaborating investigator sent a letter verifying that no adverse events had occurred during the past year.

Does tamoxifen cause DNA damage in human tissue—a collaboration between LLNL and the University of Leicester, United Kingdom.

Initiated in 1996, this study involved the administration of a single therapeutic dose of 14C tamoxifen to women who were scheduled for a hysterectomy.

Tamoxifen is a drug used in the treatment of breast cancer and, at the time of the study, was being evaluated for its use as a chemo-preventive agent in women at high risk of developing the disease.

The objective of the study was to determine whether long-term tamoxifen use would lead to increased incidence of endometrial or possible gastrointestinal tumors.

The UK has an active ethics review process which is similar to our human studies protection program. Their equivalent to our IRB is a Research Ethics Committee (REC). The UK also has an Administration of Radioactive Substances Advisory Committee (ARSAC) which is similar to our Radioactive Drug Research Committee (RDRC).

Different review process

Their review process is different from ours in that they require onetime only review by the REC, unless changes are made to the research protocol. ASRAC approval, however, must be renewed on a two-year cycle.

The specific issue relevant to this study was whether the LLNL IRB should dictate human subjects protection criteria to another country with an active, ethical review process, which they believe does a good job of protecting its citizens. For example, the consent form used in the UK differed from that which would be required in the US.

UK collaborators

UK collaborators felt strongly that their consent form did a better job of informing subjects and were unwilling to change it to US norms.

In the end, although not all required elements of 45CFR46.116 were included, the IRB determined the REC-approved consent provided sufficient information for subjects to make an informed decision and approved use of the UK form because flexibility is needed when collaborating with other nations.

Summary

Over the years, the LLNL IRB and investigators have learned some valuable lessons about collaborating with foreign institutions on human subjects research.

Key to successful foreign research collaborations involving human subjects is a willingness by collaborators from both countries to familiarize themselves and their IRB, or equivalent, with the ethical review process in each country. Doing so, up front, minimizes the frustration level which can result from different expectations and definitions.

Investigators have also noted that by communicating with the LLNL IRB early on in the process, ethical or procedural issues arising from cultural differences relating to human subjects protections can be identified and addressed, along with the methodological ones, during the protocol development process. Everyone involved in the process wants to avoid a research plan that is not workable or approvable from the IRB's perspective.

And finally, the IRB has learned that a certain level of trust is imperative in working with foreign collaborators and review boards.

Taking an imperialistic or paternalistic attitude towards international collaborations does not lead to better, or even more appropriate, human subjects protection. The lesson learned is that cultural differences can and often do result in a different, but equivalent process for assuring human research subjects protections.

The LLNL IRB must balance its responsibilities for obeying US rules and regulations with the acknowledgment that other countries may have an equally appropriate, although different process for assuring the protection of human research subjects.Δ

Taking an imperialistic or paternalistic attitude toward international collaborators does not lead to better or more appropriate human subjects protection.

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Human subjects

Collaborative IRB training Initiative

With more at stake than ever before, IRBs and investigators are under enormous pressure to closely monitor the conduct of the research.

The CITI program now includes over 200 participating institutions.

By Paul Braunschweiger, Ph.D.
Professor of Radiation Oncology and Director, University of Miami Office of Research Education and
Karen Hansen, Director, Institutional Review Office, Fred Hutchinson Cancer Research Center

The Collaborative IRB Training Initiative (CITI) began in April 2000 as a joint project between the University of Miami and Fred Hutchinson Cancer Research Center.

To raise the awareness of the biomedical research community about ethical issues and responsibilities, the U. S. Public Health Service announced a new policy in June 2000 requiring all PHS–supported researchers with significant involvement in human subjects research to provide evidence that they have participated in an educational program focused on protection of human research subjects.

By June 2000, CITI became a multi-institutional collaboration with the goal of creating a high-quality educational program to meet the federally mandated October 1, 2000 deadline.

Because the program needed to reach people around the country and around the world in a cost– and time–efficient manner, a web–based system was chosen.

More comprehensive

Although an NIH–sponsored web–based tutorial on the human subjects protection was available at the time and many institutions used this resource, the CITI collaborators believed that a more comprehensive, in–depth review of the ethical and regulatory issues was what the policy makers had in mind when the June 2000 Public halth Service (PHS) requirement was drafted.

Remarkably, over the period of about 8 weeks, a 13-module course was written, edited, revised, adapted to a web-based platform, and peer reviewed. Through the generous financial support of the University of Miami and the Fred Hutchinson Cancer Research Center and the dedicated efforts of the content authors, the first version of the CITI Course on The Protection of Human Research Subjects was launched on September 3, 2000.

The CITI Course is now available to employees at over 200 institutions including all Veterans Administration employees and all faculty and staff in the State University of New York (SUNY) system. More than 16,000 learners have registered for the course, and anonymous user surveys have indicated a high degree of satisfaction with the course content and CITI's web–based model as a solution to the PHS education mandate.

During the past several years a number of research subjects have died as a result of inappropriate procedures or actions. These high-profile incidents were not only tragedies for the subjects' families, but they were also devastating to the institutions, demoralizing to their staffs, and damaging to the careers of the researchers.

Today's biomedical research environment is complex. With more at stake than ever before, IRBs and

investigators are under enormous pressure to closely monitor the conduct of the research.

Novel ethical dilemmas

Clinical investigators often must recognize and manage novel ethical dilemmas while conducting the difficult task of extracting new knowledge from the most difficult of biological models—human beings. For example, the molecular biology revolution begun in the 1980s, and the ensuing advances in technology have spawned heated debate on maintaining confidentiality of genetic information; the avoidance and/or management of conflict of interest; and the appropriateness of certain types of human subjects research.

CITI and DOE have agreed to make the course on protection of human subjects available to all investigators and staff involved in the DOE human subjects program in Spring 2002.

CITI will provide a new course site for DOE. It will focus on history and ethical principles; regulations and process; informed consent; social/behavioral research; records-based research; genetics research; and research with investigational drugs, devices and biologics.

Additional sections

Other parts will focus on research with protected populations such as prisoners, minors, minorities, pregnant women, and fetuses in utero. Because many DOE projects involve workers and studies of the workplace environment, the DOE course site will feature an additional section on these areas.

Each module will also have a short quiz designed to assess how well learners receive the important points in the module. Although learners will likely devote a total of 3–6 hours to the course, the web-based platform enables the user to efficiently complete the course at their leisure, over several days if necessary, using multiple logon sessions.

A unique feature of the CITI course that separates it from other computer–based or online programs for mandated training is that the CITI web–based model can include institution–specific information and policies that an institution wants the faculty and staff to review. This has been a very popular feature, and many institutions post links to their IRB home page, email links to key IRB personnel, and links to key documents such as local policies and procedures and ethical documents such as the Belmont Report.

Can include institution-specific information

Those who finish the program receive a letter of course completion that can be presented to their IRB or Compliance Office. The learner can complete a voluntary survey about the course and the learning experience. DOE users can apply for six CME/CE credits at no additional cost.

The intent of the federal education mandate goes beyond a onetime course; it includes a commitment to continuing education. To address this, CITI will launch a new course site in February 2002. It will complement the current CITI course and extend the learner's understanding of key issues through completion of case studies and scenarios designed to help the learner recognize and respond to problem areas. This continuing education site will also be made available to DOE–supported researchers and staff.Δ

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New course site for DOE will focus on history and ethical principles, regulations and process, informed consent, social/behavioral research, genetics research, and more.

Responsible mandates for integrity

(Continued from page 5)

Research institutions should seize the suspension of the RCR mandate as a golden opportunity to take the matter into our own hands.

effectively requires strong conviction, not grudging compliance.

I think that NIH and ORI implemented these mandates for the right reasons: To draw attention to the importance of the responsible conduct of research and to foster a more ethical research climate, both of which are important and worthy goals that I endorse wholeheartedly.

Repeated warnings

But the problem cannot be solved by Washington; it can only be solved by researchers. Unfortunately, as ORI makes clear in the introduction to its mandate, the research community has been repeatedly warned since at least 1989 that it had to broaden RCR training.

Most research institutions and scientists failed to step up to the plate, and Washington was finally forced to use its big stick to get our attention. It worked. They got our attention.

Now research institutions should seize the suspension of the RCR mandate as a golden opportunity to take the matter into our own hands.

Training is needed

Researchers should band together to tell the government that RCR training is needed, but it need not be mandated. We should make a firm commitment to providing excellent training and showing clearly that our training is effective.

Research institutions should pledge to work together to develop standards and probably some kind of RCR certification process.

A true commitment to research integrity and education in the responsible conduct of research can only come from researchers, not the government.Δ

Social and behavioral studies

(Continued from page 8)

It became clear that attempting to regulate training requirements would not produce the results we desired.

professional organizations has organized the RCREC.

Cross-sector collaboration

RCREC was created to coordinate a cross-sector collaboration for developing education standards and outcome measures.

This group could also promote a culture conducive to the responsible conduct of research and facilitate development of standards tailored to professional practices in all disciplines, including social and behavioral studies.

For a copy of the charter or to become a member of the RCREC, please contact Daniel Vasgird at dvasgird@brooklyn.cuny.edu.

(Caroline Miner is a member of the National Human Research Protections Advisory Committee (NHRPAC) Working Group on Social and Behavioral Science (SBSWG), Cochair of the Human Subjects Research Subcommittee (HSRS) Working Group on Non-Biomedical Sciences (NBMWG), and interim council member of the RCREC.

Protecting Human Subjects

This newsletter is designed to facilitate communication among those involved in emerging bioethical issues and regulatory changes important to both DOE and the human subjects community.

DOE Human Subjects Program Manager
Dr. Susan L. Rose

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This newsletter is available at no cost to anyone interested or involved in human subjects research at DOE. Please send name and complete address (printed or typed) to the address below. Please indicate whether information is to
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Meetings

DOE—THE COMMUNITY IRB MEMBER: NEIGHBOR & PARTNER

April 8–9, 2002
Hilton Washington D.C. North • Gaithersburg, MD

Sponsored by the U.S. Department of Energy (DOE).
Community IRB members, critical to the protection of human subjects, are a nationwide resource that needs to be acknowledged and strengthened. This meeting will focus on finding and educating organizations with potential to provide new community members. It will highlight success stories of community members and IRB administrators, and explore unmet needs and issues among community members. The concept of "community" will also be explored. It is organized and chaired by Susan Rose, manager, DOE Human Subjects Program, and cochaired by Melinda Hurst, University of Southern California IRB community member.

For information about the conference, including the agenda, speakers, online registration, and hotel, see: *http://www.orau.gov/communityirb/*

BERYLLIUM RESEARCH SYMPOSIUM: BASIC MECHANISMS AND HUMAN HEALTH

June 25–26, 2002
National Library of Medicine • Bethesda, MD

Sponsored by DOE's Office of Biological and Environmental Research in cooperation with the National Institute for Occupational Safety and Health and the National Jewish Medical and Research Center.

Scientists from all disciplines are invited to this open workshop. The symposium will focus on basic science research and state-of-the-art techniques that will advance our understanding of beryllium hypersensitivity and disease. Plenary speakers are experts in selected areas of immunology and immunopathology that are closely related to beryllium disease. Minisymposia topics will include physico-chemical properties of beryllium, gene-exposure interactions, immunopathology of sensitization and disease, the biology of ultrafine particles, development of animal models of granulomatous disease, novel therapeutics, round table discussion of the ethical, legal, and social implications of beryllium research.

For more information, contact Mya Sadler, 303/398-1187.
For online information, see *www.ornl.gov/meetings/beryllium/*
For hotel information, call 800/456-7263.

PRESIDENT'S COUNCIL ON BIOETHICS

Washington, D.C.

Please consult the federal register for meeting notices of the newly formed President's Council on Bioethics. The Council is charged, among other things, with conducting fundamental inquiry into the moral and human meaning of developments in biomedical science and technology.

CONFERENCE SCHEDULE AND AGENDAS

A listing by Barnett International of several human subjects and clinical research training and educational programs can be found at this web site:
http://www.barnettinternational.com/con_schedule.asp
The site has meeting information covering several months. The programs range from "Phase IV clinical research" to "cost management in clinical trials" and "adverse events."
For more information, contact 800/856-2556

PROTECTING HUMAN SUBJECTS

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